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What's Next in the Dapivirine Ring Licensure Program?

MTN Regional Meeting

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John Steytler, MBChB, IPM Director Medical Safety

Developing HIV Prevention Products for Women worldwide

Presentation Outline

- Dapivirine ring: Regulatory update
- Additional ring research
- Planning for potential access
- Expanding women's options: Follow-on rings

Dapivirine Ring: Regulatory Update

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Complex Regulatory Process

- **Many countries have different application formats**
  - Same types of data required, from early preclinical lab tests through efficacy studies
  - Review timelines vary across regulatory agencies
- **IPM's master dapivirine ring dossier allows customized applications to specific global and African NRAs**
  - 13 years of data and findings from nearly 250 studies
  - Contains 260K PDF pages — enough to fill a 2x2 meter room printed!

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Regulatory Overview

European Medicines Agency (EMA)

- Scientific opinion on use of a product in developing countries (via Article 58 procedure)
- Submitted June 2017; currently under review

World Health Organization (WHO)

- EMA Article 58 streamlines process to potential prequalification (PQ)

African National Regulatory Authorities (NRAs)

- Following potential WHO PQ, first submissions to Kenya, Malawi, Rwanda, Tanzania, Uganda, Zimbabwe

US Food and Drug Administration (FDA)

- Planned submission early 2020

South African Health Products Regulatory Authority (SAHPRA)

- Planned submission 2020

WHO PQ – key facts:

- ✓ Facilitates access to a drugs that meet global standards for quality, safety, efficacy
- ✓ Evaluates whether products meet global manufacturing standards
- ✓ Many African NRAs consider EMA's scientific opinion and WHO PQ status in their own reviews
- ✓ Could facilitate national policy development

Projected Regulatory Timelines

2016	2017	2018	2019	2020	2021	2022

Phase III results

Open-label extension results

EMA Article 58 review

SAHPRA review

WHO guidelines and PQ

Other African NRA reviews

US FDA review

African adolescents safety & acceptability study

Safety & acceptability studies in pregnant & breastfeeding women *(planned)*

Note: Timelines are subject to change

Additional Ring Research

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IPM-MTN Collaboration: Ongoing trials

Why REACH?

- **Sub-analysis of younger women ages 18-21 in Phase III trials saw:**
  - Lower/no HIV-1 risk reduction
  - Lower adherence
  - Higher STI rate

- **Additional safety, tolerability and acceptability data on dapivirine ring and oral PrEP among young women ages 16-21**
- **Possible insight into product preferences and motivators/barriers to use**

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Women's Needs Vary During Their Lives

- **Women's circumstances—and prevention needs—change over time**
  - For women wanting contraception
  - For women wanting to conceive
  - For women who are pregnant or breastfeeding

1 in 4 pregnancy-related deaths in sub-Saharan Africa due to HIV/AIDS

IPM-MTN Collaboration: Planned trials

MTN-042 (DELIVER)

Phase IIIb, randomized, open-label safety trial of DVR and PrEP use in pregnant women

deliver

A Study of PrEP and the Dapivirine Ring in Pregnant Women

MTN-043 (B-PROTECTED)

Phase IIIb, open-label, mother-infant pair, pharmacokinetic trial, with 12 weeks of DVR use in breastfeeding

Breastfeeding PrEP & Ring Open-label Trial

B PROTECTED

Why these clinical trials are important:

- **Collect safety data among these key populations**
- **Inform potential label change**
- **Assist clinicians with benefit-risk considerations**

Planning for Potential Access

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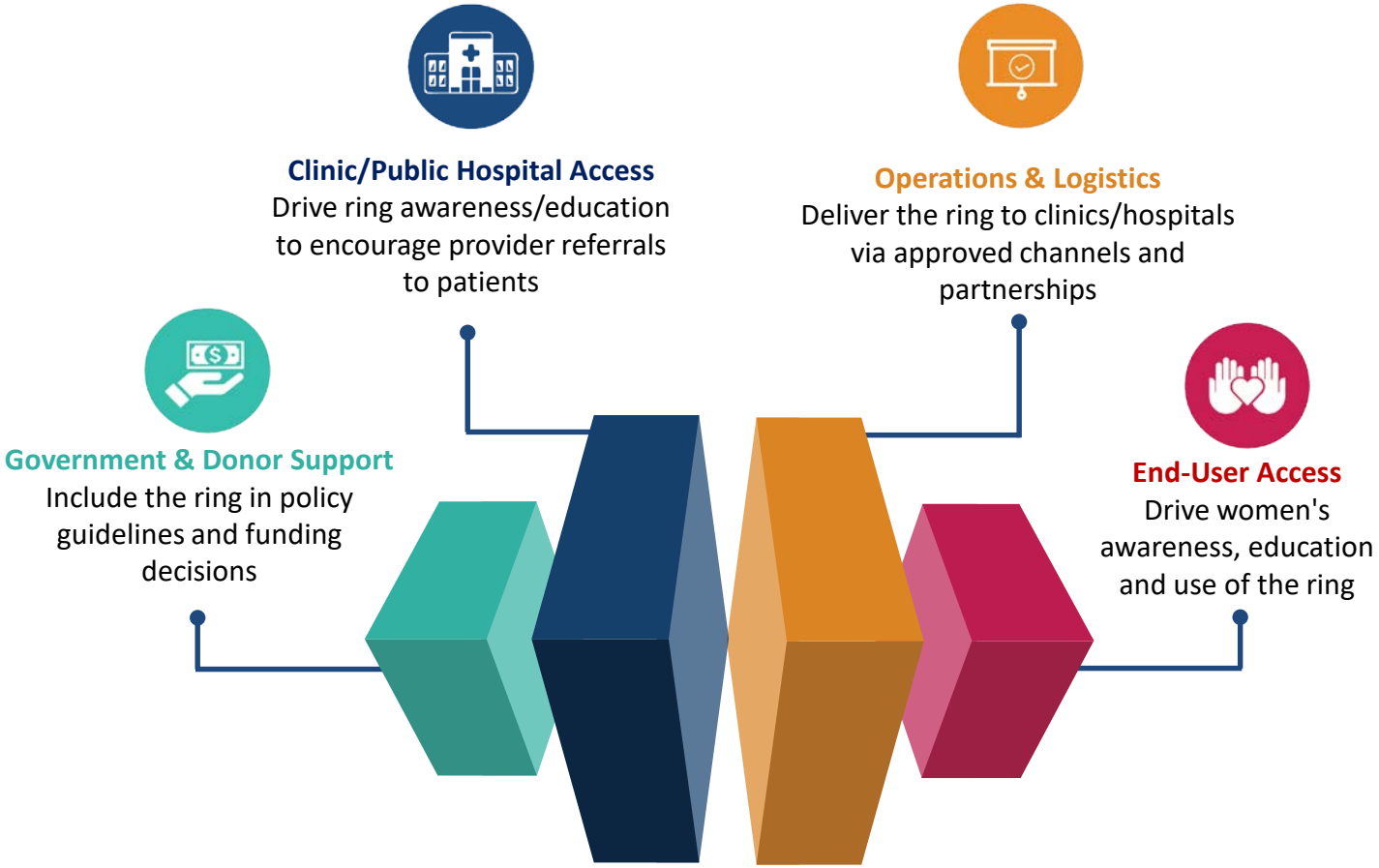
Access Strategy: Goals



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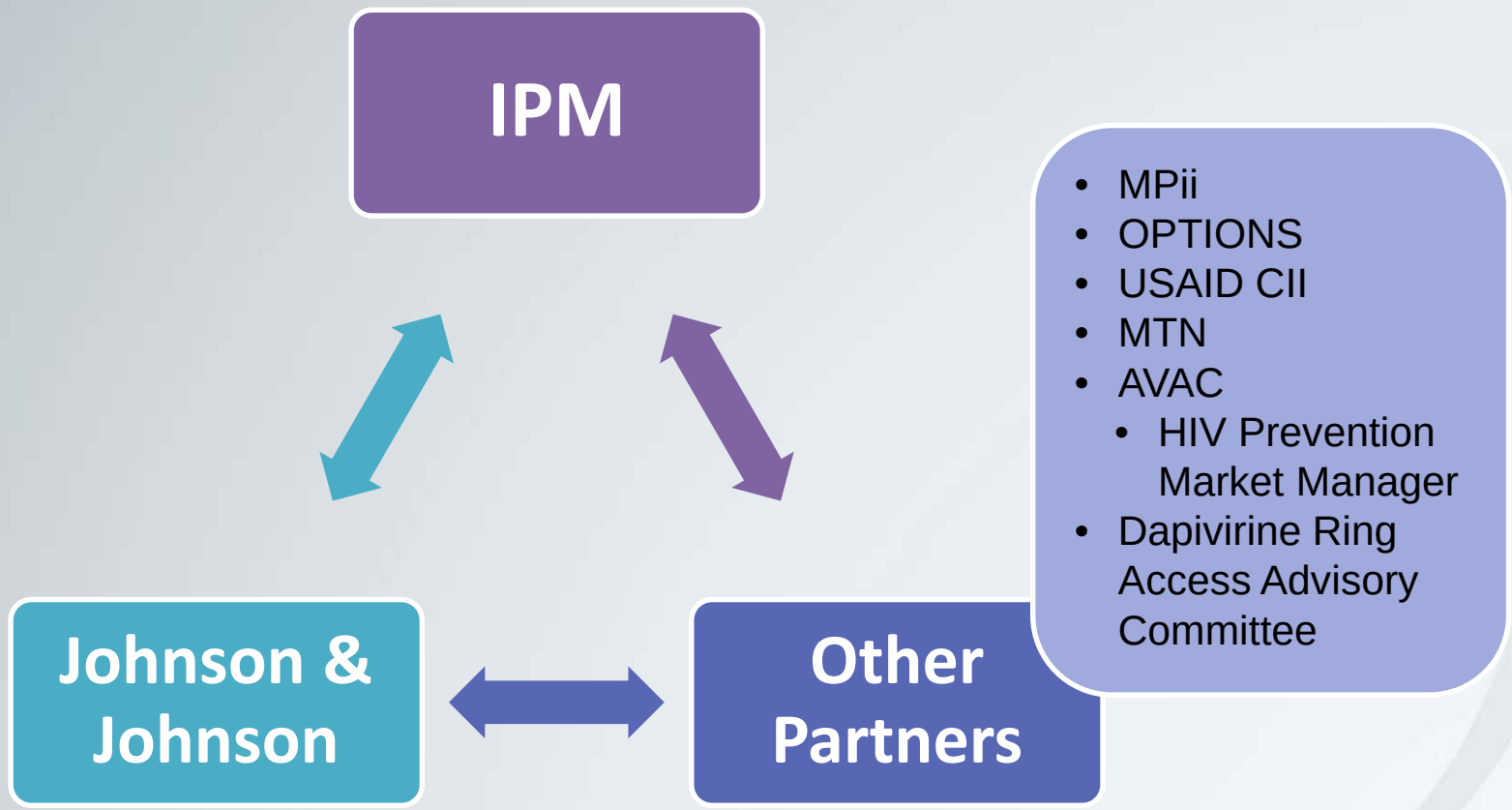
Access Collaborations for Successful Product Introduction



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Expanding Women's Options: Follow-on Rings

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Longer-acting Prevention:
IPM's 3-month dapivirine-only ring

- Could expand women's long-acting prevention options
- Lower annual costs as only 4 rings needed per year
- **MTN-036/IPM 047: Phase I safety and PK study**
  - Compare PK of two extended-use dapivirine rings (100mg and 200mg) with monthly dapivirine ring (25mg) used for 13 continuous weeks
  - Compare safety of all three rings
  - Initiated 2017; results expected 2019
  - First step in a bridging strategy

3-month Dapivirine Ring: Regulatory plans

Pending Phase I results and approval of monthly dapivirine ring, leverage efficacy data from Phase III trial(s) of monthly ring:

- Conduct bridging trial to meet regulatory requirements for establishing efficacy without full Phase III trial
- Shorten time to potential regulatory approval

Multipurpose Prevention: IPM's 3-month dapivirine-levonorgestrel ring

- Long-acting 3-month protection against HIV and unintended pregnancy
- May be more appealing and acceptable to women
- Lower annual costs compared to monthly ring
- **Clinical status:**
  - First Phase I trial (14-day use) completed: Well-tolerated, encouraging drug levels in blood, vaginal fluid
  - Second Phase I trial (90-day use) ongoing
- **Formulation optimization studies underway**
  - Exploring improvements on manufacturability and physical characteristics

MTN-044/IPM 053/CCTN 019: Second Phase I MPT ring trial

- **Initiated 2018; safety and PK trial of dapivirine-levonorgestrel ring used over 90 days**
- **Overall safety profile and bleeding patterns observed to date show an acceptable profile**
- **Some reports of post-use discoloration observed during the trial**
  - Experiments with simulated menstrual fluid produced similar observations
- **Results expected 2020**

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Questions?

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